The sole basis for rejection of claim 14-17, 19, 21-22 and 26-31 is under 35 U.S.C. § 102(a) for anticipation over Gasman, *et al., J. Biol. Chem.* (1998) 273:16913-16920. Respectfully, applicant does not believe that Gasman teaches the methods of the rejected claims.

In order for there to be anticipation, a single reference must teach each and every claim limitation in an identical manner. For a process to be anticipated, the identical process must be disclosed in a single cited document. Respectfully, Gasman does not disclose the process set forth in the rejected claims, which involve comparing protein localizations under normal and stressed conditions.

As further explained below, the only experiments described by Gasman to study the effects of external stimuli are performed on cell lysates by separation techniques.

The Office is correct that Gasman teaches, as shown in Figure 3, the intracellular distribution of RhoA in association with chromogranin A (CGA). This association was shown in cells that were fixed using a confocal microscope. Detection was through immunofluorescence where each of RhoA and CGA was coupled through antibody linkages to a fluorescent compound. This is the only application of the use of fixed cells or microscopy in this paper.

Claim 14 is directed to a method to identify an antidote for a toxic compound which requires a number of observations of patterns of localizations such as that set forth in Figure 3 of Gasman, not just one. The claim requires observation of the localization pattern of at least one signal transduction protein 1) in the presence of a toxic compound, 2) in the absence of a toxic compound and 3) in the presence of both a toxic compound and a candidate antidote. It appears that RhoA may be considered a signal transduction protein, but the observations on fixed cells using

microscopy do not include treating the cells with any toxins, much less toxins plus a candidate antidote. Specifically, Figure 3 shows multiple images, but it does not show cells under multiple conditions: from the description, it is a double-labeling experiment wherein the cells were treated with antibodies to both RhoA and CGA. The top row of photomicrographs shows one magnification, and the lower row shows a "higher magnification" (see description under Fig. 3). The first column shows the fluorescence detected for the anti-RhoA antibody and the second column shows the fluorescence detected for the anti-CGA antibody. The third column images were apparently created by pixel selection from the first two images in the same row (see Fig. 3 description, and Pg. 16916, where Fig. 3, C and F are described as "the mask constructed from the dots..."). Thus Figure 3 in Gasman, depicts cells under *only one set of conditions* and cannot anticipate claims requiring determination and comparison of protein localizations under multiple sets of conditions. Therefore, the method of claim 14 is not anticipated by Gasman.

Claim 17 is directed to a method to identify a compound potentially useful to treat a disease condition. The method also involves a number of observations including observing the intracellular localization of at least one signal transduction protein in 1) the presence and 2) the absence of a candidate compound and observing the intracellular localization pattern of the signal transduction protein in 3) the presence of an inhibitor known to inhibit a cellular function. The observations in Figure 3 do not involve including a candidate compound or including an inhibitor known to inhibit a cellular function.

Claim 19 is directed to a method to identify a therapeutic protocol which requires providing intracellular localization profiles of a *multiplicity* of signal transduction proteins characteristic of a

disease or condition as well as a localization profile of a *multiplicity* of signal transduction proteins in normal cells. At best, the sole observation on fixed cells by microscopy in Gasman involves providing a baseline observation with respect to only one signal transduction protein (RhoA) under normal conditions: it provides no intracellular localization profile of a multiplicity of signal transduction proteins even under normal conditions and no localization profile at all under conditions characteristic of a disease.

The Office points out that Gasman describes studies of the effect of mastoparan and GAP-43 on secretory granule associated phosphatidyl inositol for kinase activity. However, even if mastoparan or GAP-43 might be classified as a toxin or candidate compound, their intracellular localizations were evaluated using various methods to physically separate the components of lysed cells rather than using microscopy to observe intracellular localizations in fixed whole cells. The Office also notes that the effects of LY294002 and quercetin were evaluated; but these, too, were evaluated by physically separating the components of lysed cells, not by using microscopy on intact cells. The further studies involving mastoparan and anti-$G_{\alpha 0}$ antibodies are similarly unrelated to any studies that involve either fixed whole cells or microscopy.

Therefore, Gasman does not anticipate the present invention. Gasman fails to describe any experiments using either fixed cells or microscopy other than the simple association of RhoA with CGA.

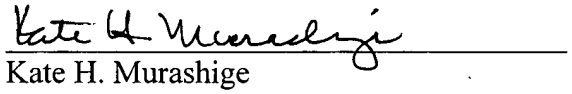
The applicant expects that the Office can cite many references in which experiments like those in Gasman are reported; such methods are commonly used to determine the subcellular location of a protein. As the foregoing demonstrates, though, merely determining which protein is

where inside a cell does not anticipate the claimed invention, even if microscopy is used: the claims are directed to methods to determine whether a compound or treatment protocol can restore normal (or more normal) protein localizations in cells that have abnormal protein localizations due to stress such as a disease condition or exposure to a toxin. Anticipation of the claimed method, therefore, *at least* requires determining protein localizations under normal conditions and under conditions involving some type of stress, and determining whether another set of conditions (e.g., a treatment protocol or compound to be evaluated) partially or wholly restores normal protein localization. References that only determine where a protein is localized, like Gasman, do not anticipate the claims.

Applicant therefore respectfully requests reconsideration of the rejection of claims 14-17, 19, 21-22 and 26-31.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512010410.

Respectfully submitted,

Dated: January 20, 2005 By: 

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